I. AMENDMENTS

This listing of claims will replace all prior versions, and listings, of claims in the application:

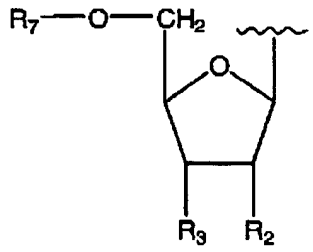
Claims 1 – 55. (Canceled).

56. (Currently Amended) A method for inhibiting the proliferation of a hyperproliferative neoplastic cell that endogenously overexpresses thymidylate synthase, comprising contacting the cell with ~~a 5'-phosphoryl or phosphoramidatyl substituted prodrug of a 5-substituted pyrimidine nucleoside or nucleotide, a derivative or a metabolite thereof that is selectively converted to a toxin in the cell by an endogenous, intracellular enzyme~~ a compound of claim 62 or a metabolite thereof formed after administration to a subject.

57. (Currently Amended) A method for treating a pathology characterized by hyperproliferative neoplastic cells that endogenously overexpresses thymidylate synthase in a subject comprising administering to the subject ~~a 5'-phosphoryl or phosphoramidatyl substituted prodrug of a 5-substituted pyrimidine nucleoside or nucleotide, a derivative or a metabolite thereof that is converted to a toxin in a hyperproliferative cell by an intracellular enzyme that is endogenously overexpressed or over-accumulated in the cell~~ a compound of claim 62 or a metabolite thereof formed after administration to a subject.

58. (Canceled).

59. (Currently Amended) The method of claim ~~58~~ 56 or 57, wherein Q has the formula:



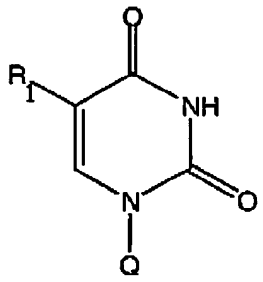
~~wherein R_2 is selected from the group consisting of a masked phosphoryl moiety and a phosphoramidatyl moiety, and wherein R_2 and R_3 are the same or different and are independently -H or -OH.~~

60. (Currently Amended) The method of claim 56 or 57 ~~claim 58~~, wherein R_1 is a halogen.

61. (Currently Amended) The method of claim 56 or 57 ~~claim 58~~, wherein R_1 is of the formula $(-CH=CH)_n-R_4$, wherein n is an integer from 1 to 10, and R_4 is selected from the group consisting of ~~H a halogen, alkyl, alkenyl, alkynyl, hydroxyl -O-alkyl, -O-aryl, O-heteroaryl, -S-alkyl, -S-aryl, -S-heteroaryl, $-NH_2$, -NH-alkyl, $-N(alkyl)_2$, -NHCHO, -OCN, -SCN, $-N_3$, -NHOH, -NHO-alkyl, and $NHNH_2$~~

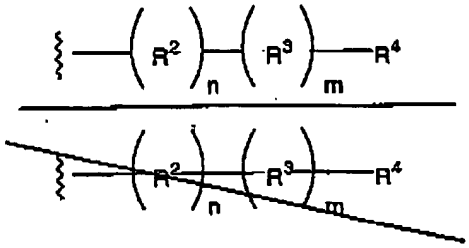
H; hydroxyl; a halogen; -NHCHO; -OCN; -SCN; $-N_3$; $-NH_2$; -NHOH; - $NHNH_2$ and a C_2 to C_4 carbon-containing substituent selected from the group consisting of alkyl, alkenyl, alkynyl, -O-alkyl, -O-aryl, O-heteroaryl, -S-alkyl, -S-aryl, -S-heteroaryl, -NH-alkyl, $-N(alkyl)_2$ and NHO-alkyl.

62. (Currently Amended) A compound of the formula:



wherein:

R^1 is of the formula:

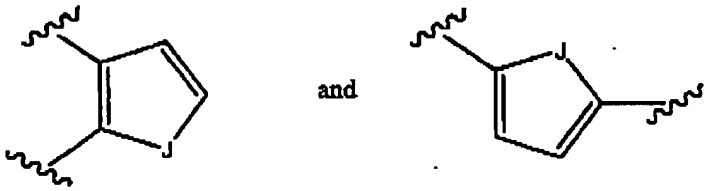


wherein R^2 is one of:

an unsaturated C_2 to C_4 hydrocarbyl group;

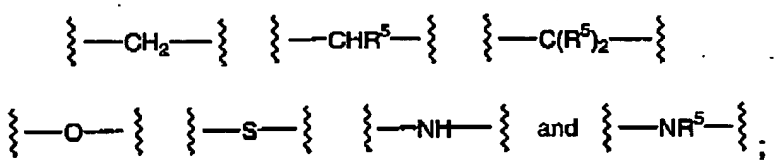
an aromatic C_4-X hydrocarbyl group, wherein X is the heteroatom; or

a heteroaromatic group having the structure:



wherein J is -O-, -S-, -Se-, -NH-, or $-NR^{ALK}-$, wherein R^{ALK} is a linear or branched alkyl having 1 to 10 carbon atoms or a cycloalkyl group having 3 to 10 carbon atoms;

R^3 is selected from the group consisting of:

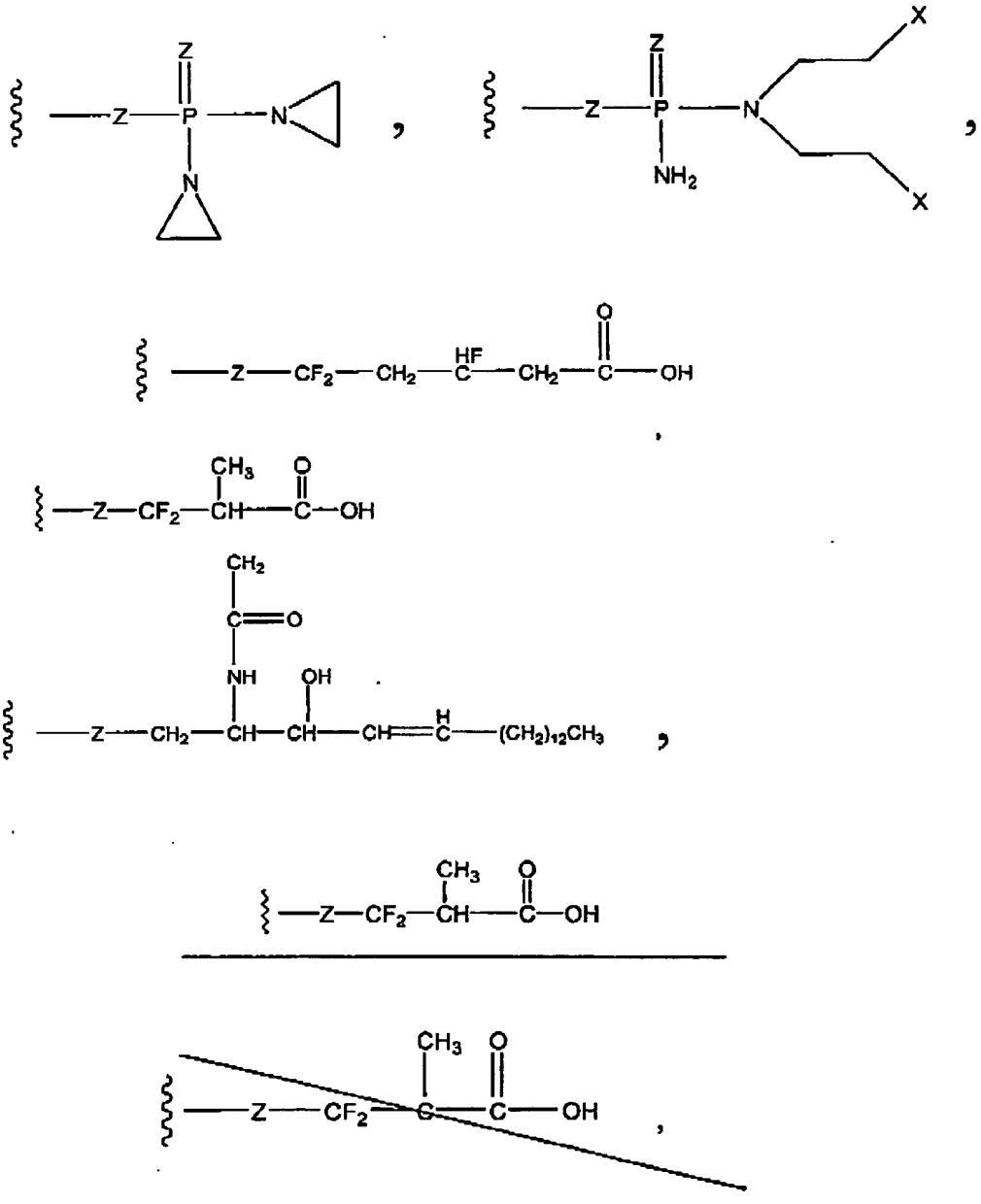


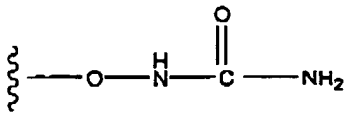
wherein R^5 may be the same or different and is independently a linear or branched alkyl group having from 1 to 10 carbon atoms, or a cycloalkyl group having from 3 to 10 carbon atoms;

wherein n is an integer from 1 to 10;

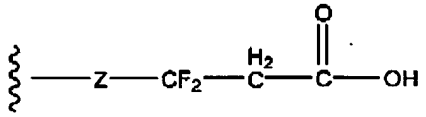
wherein m is 0 or 1;

wherein R^4 is a toxophore selected from the group consisting of:





and



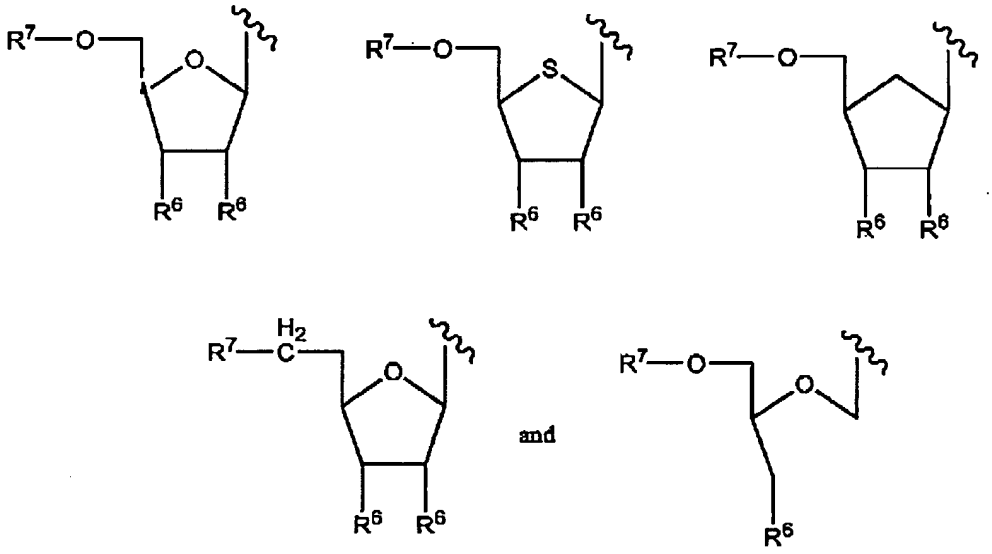
;

wherein X is -Cl, -Br, -I, or other halogen ~~potent leaving group~~, with the proviso that when R^7 is -H, and M is zero, then R^4 is not a halogen or when m is zero and n is zero, then R^4 is not a halogen;

wherein Y is independently -H or -F;

wherein Z is independently -O- or -S-;

wherein Q is selected from the group consisting of:



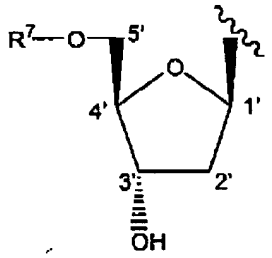
and

wherein R^6 is independently -H, -OH, $-OC(=O)CH_3$, or -O-Rg wherein Rg is a hydroxyl protecting group other than acetyl; and,

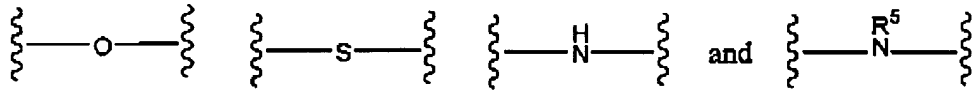
wherein R^7 is ~~selected from the group consisting of~~ hydrogen, ~~a masked phosphoryl moiety and~~ or a phosphoramidatyl derivative of a naturally-ocurring amino acid ~~moiety~~;

and wherein said compound may be in any enantiomeric, diasteriomeric, or stereoisomeric form, consisting of a D-form, L-form, α-anomeric form, and β-anomeric form.

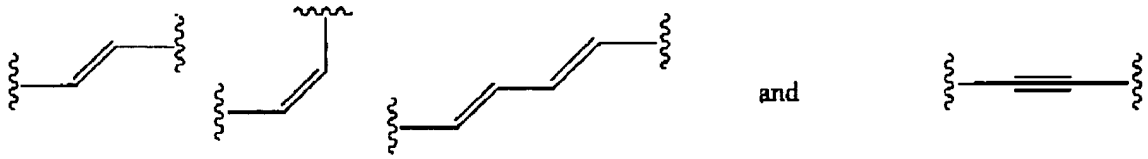
63. (Original) A compound according to claim 62, wherein Q is:



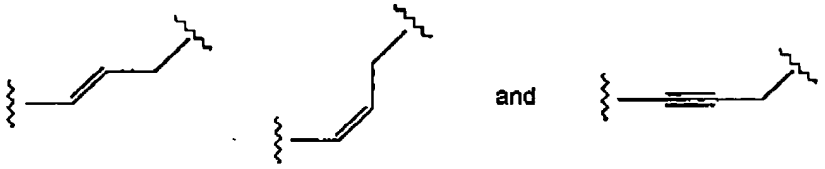
64. (Previously Amended) A compound of claim 62, wherein R^3 is selected from the group consisting of:



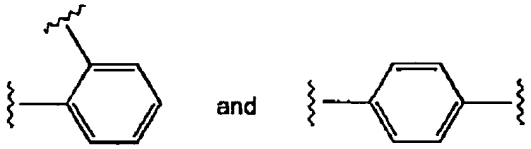
65. (Previously Amended) A compound of claim 62, wherein R^2 is selected from the group consisting of:



66. (Original) A compound of claim 62, wherein R^2 and R^3, taken together form a structure selected from the group consisting of:

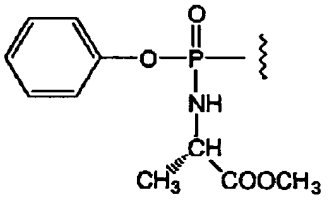


67. (Previously Amended) A compound of claim 62, wherein R^2 is selected from the group consisting of:

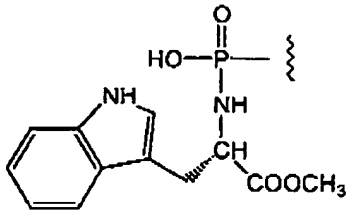


68. (Canceled)

69. (Previously Amended) A compound of claim 62, wherein R^7 is:



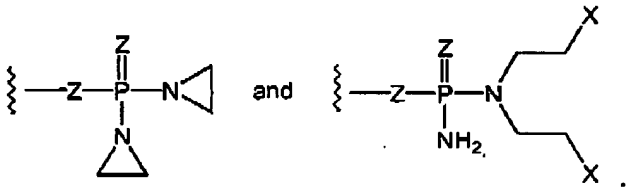
70. (Previously Amended) A compound of claim 62, wherein R^7 is:



71. (Canceled).

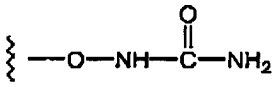
72. (Canceled).

73. (Original) A compound of claim 62, wherein R^4 is selected from the group consisting of:

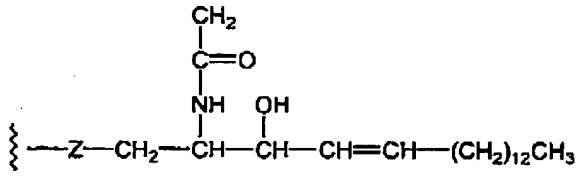


74. (Original) A compound of claim 62, wherein R^4 is selected from the group consisting of:

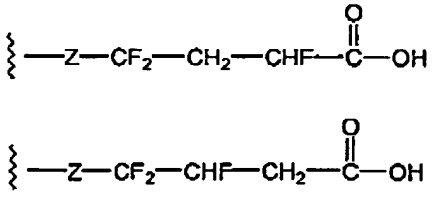
75. (Original) A compound of claim 62, wherein R^4 is:

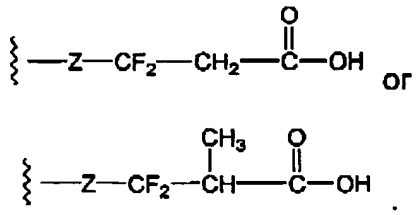


76. (Previously Amended) A compound of claim 62, wherein R^4 is:

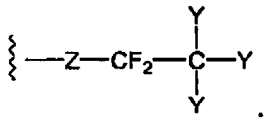


77. (Original) A compound of claim 62, wherein R^4 is:

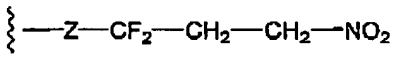




78. (Original) A compound of claim 62, wherein R^4 is:



79. (Original) A compound of claim 62, wherein R^4 is:



80. (Canceled).

81. (Canceled).

82. (Canceled).

83. (Canceled).

84. (Canceled).

85. (Canceled).

86. (Currently Amended) A method of inhibiting the proliferation of a pathological neoplastic cell that endogenously overexpresses ~~an~~ intracellular thymidylate synthase ~~target enzyme~~, comprising:

(a) contacting the cell with a compound of claim 62 or a metabolite thereof; and

(b) allowing the cell to take-up and selectively convert the compound from an inactive state to an active toxic by-product by means of the intracellular target enzyme.

87. (Currently Amended) A method of inhibiting the proliferation of a hyperproliferative cell that endogenously overexpresses intracellular ~~enzymes and which contribute~~ thymidylate synthase and wherein said overexpression also contributes to drug resistance, comprising:

(a) contacting the cell with the compound of claim 62 or a metabolite thereof that can be formed after administration; and

(b) allowing the cell to take-up and selectively convert the compound from an inactive state to an active toxic byproduct by means of the enzyme.

88. (Previously Amended) The method of claims 86 or 87, wherein the hyperproliferative cell is a cancer cell.

89. (Original) The method of claim 88, wherein the cancer cell is selected from the group consisting of a colorectal cell, a head and neck cancer cell, a breast cancer cell, a liver cancer cell and a gastric cancer cell.